

**COG-ADVL1823: Larotrectinib (LOXO-101, NSC# 788607, IND# 141824) for Previously Untreated TRK Fusion Pediatric Solid Tumors and TRK Fusion Relapsed Pediatric Acute Leukemias**

**FAST FACTS**

Eligibility Reviewed and Verified By \_\_\_\_\_

MD/DO/RN/LPN/CRA Date \_\_\_\_\_

MD/DO/RN/LPN/CRA Date \_\_\_\_\_

Consent Version Dated \_\_\_\_\_

**PATIENT ELIGIBILITY:**

**Important note:** The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

- \_\_\_ 1. Reservation - Prior to obtaining informed consent and enrolling a patient, a reservation must be made.
- \_\_\_ 2. Timing  
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible and will not be able to receive further protocol therapy.** The only exception to this is for intrathecal methotrexate, intrathecal cytarabine, or intrathecal triples, which can be given within 1 week prior to the patient's first dose of larotrectinib for patients on Part C **ONLY**. If intrathecal methotrexate, intrathecal cytarabine, or intrathecal triples are given prior to enrollment, a separate institutional consent must be obtained.
- \_\_\_ 3. Pathology and Molecular Diagnostic Report  
Immediately following enrollment, the pathology report for the diagnosis under which the patient is being enrolled and molecular diagnostic (FISH, PCR, or NGS) report confirming the presence of a TRK fusion must be uploaded into Rave. In addition, pathology reports (including reports of surgical margins) from any surgical procedures including tumor resections or tumor/metastatic/recurrent site biopsies done while the patient is on study must be uploaded into RAVE. The reports must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the reports prior to submission.
- \_\_\_ 4. **All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies and bone marrow biopsy and/or aspirate, if applicable, must be obtained within 28 days prior to start of protocol therapy (repeat the tumor imaging if necessary).**
- \_\_\_ 5. Age: Patients must be ≤ 30 years of age at the time of study entry.
- \_\_\_ 6. Diagnosis:
  - i. Cohort A: Patients must have a histologic diagnosis of infantile fibrosarcoma with an *NTRK1*, *NTRK2*, or *NTRK3* fusion identified in a CLIA/CAP certified laboratory. Fusions may be identified by FISH or molecular techniques (RT-PCR using primers flanking the fusion junction or next generation sequencing). For fusions identified by FISH, an *ETV6* rearrangement is sufficient for eligibility in Cohort A. Identification of the upstream TRK fusion partner is not required.
  - ii. Cohort B: Patients must have a histologic diagnosis of any solid tumor other than infantile fibrosarcoma, including CNS tumors but excluding high grade gliomas. An *NTRK1*, *NTRK2*, or *NTRK3* fusion must be identified in a CLIA/CAP certified laboratory. Fusions may be identified by FISH or molecular techniques (RT-PCR using primers flanking the fusion junction or next generation sequencing). For fusions identified by FISH, there must be an identified rearrangement in *NTRK1*, *NTRK2*, or *NTRK3* (e.g., an *ETV6* rearrangement is **not** sufficient for eligibility) unless the patient has a diagnosis of congenital mesoblastic nephroma in which case an *ETV6* rearrangement is sufficient for eligibility. Identification of the upstream TRK fusion partner is not required.

- iii. Cohort C: Patients must have a histologic diagnosis of relapsed or refractory acute leukemia with an *NTRK1*, *NTRK2*, or *NTRK3* fusion identified in a CLIA/CAP certified laboratory. Fusions may be identified by FISH or molecular techniques (RT-PCR using primers flanking the fusion junction or next generation sequencing). For fusions identified by FISH, there must be an identified rearrangement in *NTRK1*, *NTRK2*, or *NTRK3* (e.g., an *ETV6* rearrangement is **not** sufficient for eligibility). Identification of the upstream TRK fusion partner is not required.

7. Disease Status

- i. Solid Tumors (Cohorts A & B): Patients must have measurable disease (see Section 10.3.1 for definition). Patients must have disease that cannot be completely resected without a predicted functional, neurologic, or significant cosmetic deficit in the opinion of the investigator.
- ii. Leukemia (Cohort C): Patients must have  $\geq 5\%$  blasts in the bone marrow. Extramedullary disease is permitted.

8. Performance Level

Patients must have a Lansky or Karnofsky performance status score of  $\geq 50$ , corresponding to ECOG categories 0, 1 or 2. Use Karnofsky for patients  $> 16$  years of age and Lansky for patients  $\leq 16$  years of age. **NOTE:** Neurologic deficits in patients with CNS tumors must have been stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

(See [Appendix IX](#))

9. Prior Therapy

- Cohorts A & B: No prior anti-cancer therapy, including radiotherapy, other than surgical resection is permitted.
- Patients who experience recurrence after surgery alone and no other anti-cancer therapy will be eligible.
  - If not eligible due to prior anticancer therapy, patients may be eligible for the larotrectinib arm of Pediatric MATCH (APEC1621A) or treatment with commercial larotrectinib off study.
- Cohort C: The following apply to patients with relapsed/refractory leukemia:

Patients with relapsed leukemia (Cohort C) must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

- a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive. See DVL homepage for the Myelosuppressive, Non-Myelosuppressive, and Antibody Anti-Cancer Agents table (<https://cogmembers.org/Site/Disc/DevTherapeutics/Default.aspx>). For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.
- A waiting period prior to enrollment is not required for patients receiving standard cytotoxic maintenance chemotherapy (i.e., corticosteroid, vincristine, 6MP, and/or methotrexate).
  - A waiting period is not required for patients receiving a single dose of intrathecal methotrexate, hydrocortisone, and/or cytarabine within 7 days prior to enrollment
  - $\geq 14$  days must have elapsed after the completion of other cytotoxic therapy, with the exception of hydroxyurea, for patients not receiving standard maintenance therapy. Additionally, patients must have fully recovered from all acute toxic effects of prior therapy.

Note: Cytoreduction with hydroxyurea must be discontinued  $\geq 24$  hours prior to the start of protocol therapy.

- b. Anti-cancer agents not known to be myelosuppressive (e.g., not associated with reduced platelet or ANC counts):  $\geq 7$  days after the last dose of agent. See DVL homepage for the Myelosuppressive, Non-Myelosuppressive, and Antibody Anti-Cancer Agents table (<https://cogmembers.org/Site/Disc/DevTherapeutics/Default.aspx>). For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment

- c. Anti-cancer agents that are antibodies:  $\geq 21$  days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade  $\leq 1$ . There is an exception for blinatumomab infusions, for which patients must have been off for at least 3 days and all drug related toxicity must have resolved to Grade 2 or lower as outlined in the inclusion/exclusion criteria. See DVL Homepage for the Myelosuppressive, Non-Myelosuppressive, and Antibody Anti-Cancer Agents table (<https://cogmembers.org/Site/Disc/DevTherapeutics/Default.aspx>).
- d. Corticosteroids: See [Section 3.3.2.1](#). If used to modify **immune adverse events** related to prior therapy,  $\geq 14$  days must have elapsed since last dose of corticosteroid. A waiting period prior to enrollment is not required for patients receiving corticosteroid for leukemia therapy/cytoreduction.
- e. Hematopoietic growth factors:  $\geq 14$  days after the last dose of a long-acting growth factor (e.g. pegfilgrastim) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator.
- f. Interleukins, Interferons and Cytokines (other than Hematopoietic Growth Factors):  $\geq 21$  days after the completion of interleukins, interferon or cytokines (other than Hematopoietic Growth Factors )
- g. Stem cell Infusions (with or without TBI):
  - Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion:  $\geq 84$  days after infusion and no evidence of GVHD.
  - Autologous stem cell infusion including boost infusion:  $\geq 42$  days.
- h. Cellular Therapy:  $\geq 42$  days after the completion of any type of cellular therapy (e.g., modified T cells, NK cells, dendritic cells, etc.)
- i. XRT/External Beam Irradiation including Protons:  $\geq 14$  days after local XRT;  $\geq 150$  days after TBI, craniospinal XRT or if radiation to  $\geq 50\%$  of the pelvis;  $\geq 42$  days if other substantial BM radiation.
- j. Radiopharmaceutical therapy (e.g., radiolabeled antibody):  $\geq 42$  days after systemically administered radiopharmaceutical therapy.
- k. Patients must not have received prior exposure to TRK inhibitors (including larotrectinib, LOXO-195, entrectinib, lorlatinib, crizotinib, or lestaurtinib).

10. Organ Function Requirements

- Adequate Bone Marrow Function Defined As:
  - a. For patients with solid tumors without known bone marrow involvement:
    - Peripheral absolute neutrophil count (ANC)  $\geq 1000/\text{mm}^3$
    - Platelet count  $\geq 100,000/\text{mm}^3$  (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
    - Hemoglobin  $\geq 8.0$  g/dL at baseline (may receive RBC transfusions)
  - b. Patients with solid tumors with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in [Section 3.2.6.1.a](#) (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity.
  - c. For patients with leukemia:
    - Platelet count  $\geq 20,000/\text{mm}^3$  (may receive platelet transfusions).
    - Hemoglobin  $\geq 8.0$  g/dL at baseline (may receive RBC transfusions)
    - These patients must not be known to be refractory to red cell or platelet transfusion.

- Adequate Renal Function Defined As:
  - a. Creatinine clearance or radioisotope GFR  $\geq 70$  mL/min/1.73 m<sup>2</sup> **or** a serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
$\geq 16$ years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR utilizing child length and stature data published by the CDC.

- For patients < 1 month of age, serum creatinine levels must be < 1.5x the treating institution’s creatinine ULN for patients < 1 month of age or the creatinine clearance or radioisotope GFR must be > 70 mL/min/1.73 m<sup>2</sup>.
- Adequate Liver Function Defined As:
  - i. Patients with solid tumors:
    - Bilirubin (sum of conjugated + unconjugated)  $\leq 1.5$  x upper limit of normal (ULN) for age. After approval of the study chair or designee, infants with a higher total bilirubin due to physiologic or breast milk jaundice are eligible if the conjugated (direct) bilirubin is  $\leq 2$  mg/dL.
    - SGPT (ALT)  $\leq 135$  U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
    - Serum albumin  $\geq 2$  g/dL.
  - ii. Patients with leukemias:
    - Conjugated (direct) bilirubin  $\leq 1.5$  x upper limit of normal (ULN) for age.
    - SGPT (ALT)  $\leq 225$  U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
    - Serum albumin  $\geq 2$  g/dL.
- Central Nervous System Function Defined As:
  - Patients with seizure disorder may be enrolled if on a stable antiepileptic regimen for  $\geq 14$  days and well controlled.
  - Nervous system disorders (CTCAE v5) except tendon reflex decreased resulting from prior therapy must be  $\leq$  Grade 2.

**Assent:** The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research

## EXCLUSION CRITERIA:

- \_\_\_ 1. Pregnancy or Breast-Feeding  
Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies, *OR* because there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Female patients of reproductive potential may not participate unless they have agreed to use a highly effective contraceptive method for the duration of study therapy and for at least one month after the final dose of larotrectinib. Males of reproductive potential with a non-pregnant female partner of child-bearing potential must use a highly effective contraception for the duration of the study and for at least one month after the final dose of larotrectinib. Because of the unknown risk of larotrectinib in nursing infants, nursing women should discontinue breastfeeding during treatment with larotrectinib and for 3 days following the final dose.
- \_\_\_ 2. Concomitant Medications:
  - Corticosteroids: Patients with solid tumors, including CNS tumors, requiring corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. Patients with leukemia may receive systemic corticosteroids for cytoreduction up to 24 hours prior to the start of protocol therapy. If used to modify **immune adverse events** related to prior therapy,  $\geq 14$  days must have elapsed since last dose of corticosteroid.
  - Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.
  - Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible [except leukemia patients receiving corticosteroids or hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy]. Patients with leukemia should receive a single dose of intrathecal cytarabine, hydrocortisone, and/or methotrexate within 7 days prior to Day 1 of Cycle 1 at the time of the baseline lumbar puncture.
  - Anti-GVHD agents post-transplant: Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.
  - CYP3A4 Inducers/Inhibitors: Patients currently receiving a strong CYP3A4 inducer or inhibitor are not eligible (see [Appendix VI](#)). Strong inducers or inhibitors of CYP3A4 should be avoided from 14 days prior to enrollment to the end of the study. **Note:** CYP3A4 inducing anti-epileptic drugs and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed.
- \_\_\_ 3. Malabsorption:  
Patients with malabsorption syndrome or other conditions that significantly limit enteral absorption are not eligible.
- \_\_\_ 4. Swallow or Gastric Access:  
Patients who are unable to swallow capsules or liquid and do not have gastric access via a nasogastric or gastrostomy tube are not eligible.
- \_\_\_ 5. Infection:  
Patients who have an uncontrolled infection are not eligible.
- \_\_\_ 6. Solid Organ Transplant:  
Patients who have received prior solid organ transplantation are not eligible.
- \_\_\_ 7. Safety Monitoring:  
Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.
- \_\_\_ 8. Diagnosis:  
Patients with High Grade Gliomas (HGG) are not eligible.

**REQUIRED OBSERVATIONS:**

Required Observations in Cycle 1, Cohorts A & B

**All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.**

- a. Hx/Wt /Ht/BSA. Within 7 days prior to Cycle 1.
- b. Performance status. Prior to Cycle 1.
- c. Physical exam (including VS and neurologic examination). Prior to Cycle 1.
- d. CBC/diff/platelets: Prior to Cycle 1 and every week during Cycle 1. If patients have Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.
- e. Electrolytes including Ca<sup>++</sup>. Prior to Cycle 1.
- f. Creatinine, ALT, bilirubin. Prior to Cycle 1.
- g. Albumin. Prior to Cycle 1.
- h. Disease evaluation. Prior to Cycle 1.
- i. Pregnancy test. Prior to Cycle 1. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control.
- j. Bone marrow evaluation. Prior to Cycle 1. Bone marrow aspirate and/or biopsy should only be performed on patients with solid tumors with known bone marrow metastasis on the basis of history, symptoms, laboratory evaluation or other clinical data.
- k. Circulating tumor DNA. Prior to Cycle 1 and on Day 15 of Cycle 1. See [Section 7.3.2](#) for details.
- l. Tumor tissue submission. Prior to Cycle 1. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment. See [Section 7.3.1](#) for details.
- m. Patient diary. Uploaded into RAVE at the end of Cycle 1. See [Appendix VII-A](#) and [Appendix VII-B](#) for details.
- n. Neurocognitive assessments. Within 4 weeks after enrollment. See [Section 3.1.7](#) and [Appendix XI](#) for details.

**TREATMENT PLAN:**

<b>Treatment Schedule</b>	
<b>Days 1 – 28</b>	Larotrectinib 100 mg/m <sup>2</sup> /dose orally/NG/G-tube twice daily (maximum 100 mg/dose BID)
<b>Day 28</b>	End of Cycle

**TOXICITIES AND DOSAGE MODIFICATIONS:**

See Section 4.1.1 for Dose Reduction information.

Also see Section 5.0

**SPECIMEN REQUIREMENTS:**

See Section 7.3

Streck Tube optional prior to Cycle 1

Slides, CSF and Blood PK studies are required.

See Section 7.4 for central imaging review requirements